Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee

ABSTRACT ● **Objective** To determine the effectiveness of glucosamine in reducing pain from osteoarthritis of the knee. ● **Design** Randomized, double-blind parallel trial of glucosamine 500 mg three times daily or a placebo for 2 months. ● **Setting** Veterans Affairs Medical Center, Prescott, AZ. ● **Participants** Ninety-eight patients aged 34 to 81 being treated for osteoarthritis of the knee. ● **Main outcome measures** Pain intensity both at rest and while walking as assessed by a visual analog scale at baseline and after 30 and 60 days of treatment. ● **Results** Forty-nine patients were randomly allocated to each group. There was no statistical difference between the two groups in scores on the visual analog scale at 30 days for resting (mean [SD] score placebo group 3.5 [2.7] vs 3.3 [2.4] glucosamine group, P=0.66) or walking (5.1 [2.6] vs 5.3 [2.4], P=0.69); there was also no difference at 60 days for resting (3.4 [2.5] vs 3.2 [2.5], P=0.81) or walking (4.9 [2.2] vs 4.9 [2.8], P=0.90). There was also no statistical difference between groups in the mean change from baseline in scores on the visual analog scale (mean [SD] change for walking at 60 days placebo group −1.5 [2.5] vs glucosamine group −1.4 [3.0], P=0.77). Two participants taking glucosamine and 4 taking placebo withdrew from the study due to adverse side effects (P=0.67). ● **Conclusion** Glucosamine was no better than placebo in reducing pain from osteoarthritis of the knee in this group of patients.

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Glucosamine sulfate is widely purported in the media and on the Internet to be an effective treatment for osteoarthritis. Its popularity can be traced, in part, to the success of glucosamine in veterinary medicine and to the anecdotal reports of patients with arthritis.[1] Some controlled clinical trials have examined the efficacy of glucosamine in treating osteoarthritis.[2-6] These trials have identified some benefit in using oral or intra-articular glucosamine when compared with nonsteroidal anti-inflammatory drugs or placebo. Despite these data, glucosamine is not recommended as a treatment by the American College of Rheumatology.[7] Nevertheless, it may offer a comparatively safe alternative to nonsteroidal anti-inflammatory drugs for treating osteoarthritis, and further study is warranted, especially in veterans, who tend to be older and have more comorbidity than the general population.

PARTICIPANTS AND METHODS

Selection of participants

Patients were eligible to participate in the study if they had a history of osteoarthritis of the knee and had radiographic findings consistent with the disease. Patients were recruited by referral from primary care providers in the outpatient clinics of the medical center. Knee radiographs were graded by a radiologist who was blinded to the purpose of the study. Grading was based on criteria described by Kellgren and Lawrence.[8] Grade 0 indicated no arthropathy; grade 4, severe arthropathy. Patients who had been treated earlier with either glucosamine or chondroitin, or both, who were not ambulatory, or who had radiographic findings classed as less severe than grade 1 were excluded from the study. A human studies committee approved this study, and informed consent was obtained from all participants.

Allocation and treatment

Participants were randomly allocated in a double-blind design to treatment with either 500 mg glucosamine (Applehart Laboratories, Bedford, NH) three times daily or a placebo. Randomization was performed using a computer generated list of random numbers. Treatment lasted 2 months. Glucosamine was given with or without food. Patients who were taking other analgesics were instructed to continue them for the duration of the study.

Measurement of pain intensity

Participants were evaluated at the beginning of the study and at 30 and 60 days after starting treatment. Pain intensity was assessed with a visual analog scale. Numerous

Summary points

- Glucosamine has been reported to be effective in reducing pain in osteoarthritis
- Controlled clinical trials have found that glucosamine may be effective in treating osteoarthritis when compared with nonsteroidal anti-inflammatory drugs or placebo
- Glucosamine was no more effective than placebo after 2 months of treatment for osteoarthritis of the knee in this study of older patients

trials have validated the visual analog scale as a means of evaluating pain intensity, especially for subjective knee complaints.[9, 10] Participants were instructed to make a mark on a horizontal line that was 10 cm long to reflect the average rating of the discomfort they had experienced during the previous week. The mark on the line was measured from the left using a metric ruler; a mark at 0 was classed as "no discomfort" and at 10 cm as "severe discomfort." Participants completed two visual analog assessments at each visit, one representing pain intensity while at rest and the other representing pain while walking. Side effects were assessed at each visit by one of us (JPR) asking the patient if they had experienced any changes in their physical symptoms since the previous visit. Side effects were noted on the same form used for data collection

Data analysis

Demographic data were compared between groups using an independent Student *t* test for means (age, baseline visual analog scores, duration of arthritis) and a z test for proportional data (for example, the percentage taking nonsteroidal anti-inflammatory drugs) using SigmaStat software (Jandel, San Rafael, CA). Scores on the visual analog scale at rest and while walking were averaged, and means between treatment groups were compared at each visit using a one-way analysis of variance. Changes in scores from baseline were also computed, and the means were compared using a one-way analysis of variance. Statistical significance was set at $\alpha = 0.05$. We calculated that an absolute difference of 1.1 on the visual analog scale should be detectable if we evaluated 100 participants, assumed a standard deviation of 2, a power of 80%, and an α of 0.05.[11] The dropout rate from side effects was compared between treatment groups using a z test.

RESULTS

Altogether, 114 participants were enrolled in the study. They were well matched with respect to demographic data, duration of arthritis, baseline score on the visual analog scale, the concomitant use of analgesics, and radiographic stage (table 1). The mean (SD) age of participants in the placebo group was 64 (11) years and in the glucosamine group was 63 (12). The mean (SD) duration of arthritis in the placebo group was 14 (13) years and in the glucosamine group 12 (10). All participants met the criteria for knee osteoarthritis as described by the American College of Rheumatology.[7] Five patients in each group were lost to follow up and were not included in the analysis. Data were analyzed on 98 patients, 49 in each group.

No statistical difference was noted between the glucosamine group and the placebo group in mean scores for resting and walking at the 30-day and 60-day assessment (mean [SD] score for resting at 60 days: placebo group 3.4 [2.5] vs 3.2 [2.5] glucosamine group, P=0.81; score for walking: 4.9 [2.2] vs 4.9 [2.8], P=0.90) (table 2). There was also no statistical difference between the groups when the mean change in scores from baseline was calculated and compared (mean [SD] change for walking at 60 days: placebo group −1.5 [2.5] vs −1.4 [3.0] glucosamine group, P=0.77) (table 3). There was a similar distribution of change in scores at the 60-day assessment for both resting and walking (figures 1 and 2).

Seventeen patients (34%) taking glucosamine experienced side effects compared with 11 (23%) taking pla-

Table 1 *Demographic and baseline characteristics of 98 patients with osteoarthritis of the knee who were randomly allocated to treatment with either placebo or 500 mg glucosamine three times daily*

Characteristics	Treatment		P value
	Placebo (n = 49)	Glucosamine (n = 49)	
Number of men	46	47	
Mean (SD) age (years)	64 (11)	63 (12)	0.74
Mean (SD) duration of arthritis (years)	14 (13)	12 (10)	0.44
Mean (SD) weight (kg)	91 (15)	91 (20)	0.98
Mean (SD) score of pain intensity at baseline*:			
Resting	3.6 (2.8)	3.9 (2.4)	0.56
Walking	6.4 92.5)	6.4 (2.5)	0.96
Number (%) taking analgesics:			
NSAID	16 (32)	17 (34)	0.99
Acetaminophen	10 (20)	8 (16)	0.80
Hydrocodone and acetaminophen	2 (4)	3 (6)	0.99
Number (%) at each radiographic stage:			
Grade 1	15 (30)	19 (40)	0.46
Grade 2	9 (19)	9 (18)	0.86
Grade 3	17 (35)	17 (35)	0.81
Grade 4	8 (16)	3 (7)	0.35

NSAID = nonsteroidal anti-inflammatory drugs
*Pain intensity was measured with a visual analog scale; a score of 0 indicated "no discomfort" and a score of 10 indicated "severe discomfort."

Table 2 *Scores of pain intensity as measured with a visual analog scale**

Mean (SD) score	Treatment Placebo (n = 49)	Glucosamine (n = 49)	P value
At 30 days:			
Resting	3.5 (2.7)	3.3 (2.4)	0.66
Walking	5.1 (2.6)	5.3 (2.4)	0.69
At 60 days:			
Resting	3.4 (2.5)	3.2 (2.5)	0.81
Walking	4.9 (2.2)	4.9 (2.8)	0.90

*A score of 0 indicated "no discomfort" and a score of 10 indicated "severe discomfort."

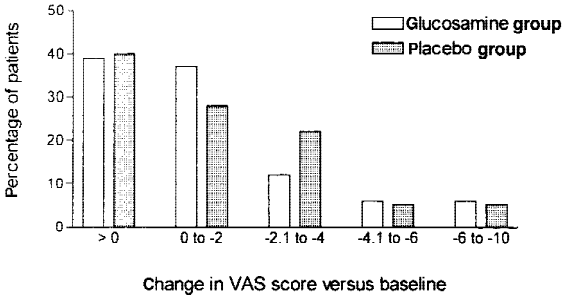

Figure 1 Distribution of changes in scores of pain intensity at rest (60-day visit), as measured by a visual analog scale (VAS) among patients with osteoarthritis of the knee. A score of 0 indicates "no discomfort" and 10 indicates "severe discomfort."

cebo. Most side effects in both groups were mild and self-limiting; side effects included loose stools, nausea, heartburn, and headache. Two participants taking glucosamine withdrew from the study because of side effects. One patient had significant diarrhea and the other, dizziness. Side effects subsided after treatment was stopped. Four participants in the placebo group also withdrew because of side effects which included rash, sedation, diarrhea, and constipation. The rate of withdrawal as a result of side effects was not statistically different between the groups (P=0.67) (data not shown).

DISCUSSION

In this study glucosamine had little effect on the intensity of pain in patients with osteoarthritis of the knee. This is the first study to report negative findings in the use of oral glucosamine to treat osteoarthritis, and thus our findings contradict those reported in other prospective trials of this treatment. One trial of 200 patients showed that glucosamine 1.5 g/day was as effective as ibuprofen 1.2 g/day in bringing about a reduction in pain scores on the Lequesne index.[2] A trial of 40 patients with osteoarthritis of the knee found that glucosamine 1.5 g/day was statistically superior to ibuprofen 1.2 g/day in reducing pain scores at 8 weeks.[3] Glucosamine was less effective than ibuprofen when patients were assessed at 4 weeks. The largest study included 252 patients and found that glucosamine 1.5 g/day was superior to placebo in reducing pain scores on the Lequesne index.[4]

It is not clear why there is disagreement between the results of our study and those of previous investigations. In this study, patients tended to be older, heavier, and had had arthritis longer than participants in other trials, suggesting that our patients had more pronounced arthropathy, which can be seen when radiographic findings from this study are compared to the largest placebo-controlled study.[4] Although methods of grading knee radiographs differed slightly between studies, more patients in our study had more severe disease than patients in other studies, suggesting more pronounced joint pathology. It is possible that patients with more severe disease may not respond as readily to glucosamine as patients with less severe arthropathy. This would make theoretical sense in that glucosamine is believed to be a precursor of proteoglycans. Proteoglycans are thought to be instrumental in helping cartilage retain water and in promoting formation of an elastic layer, factors which may improve the functional characteristics of cartilage.[12] Older patients with a longer history of arthritis may have more damage to their

Table 3 *Mean change from baseline in score of pain intensity as measured with a visual analog scale**

Mean (SD) change	Treatment Placebo (n = 49)	Glucosamine (n = 49)	P value
At 30 days:			
Resting	0.18 (2.5)	0.71 (2.3)	0.28
Walking	1.2 (2.6)	1.1 (2.0)	0.91
At 60 days:			
Resting	0.59 (2.9)	0.73 (2.7)	0.81
Walking	1.5 (2.5)	1.4 (3.0)	0.77

*A score of 0 indicated "no discomfort" and a score of 10 indicated "severe discomfort."

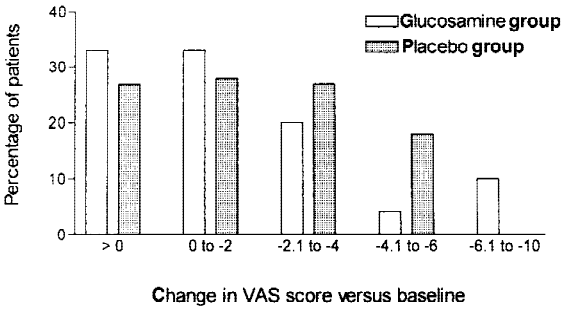

Figure 2 Distribution of changes in scores of pain intensity while walking (60-day visit), as measured by a visual analog scale (VAS) among patients with osteoarthritis of the knee. A score of 0 indicates "no discomfort" and 10 indicates "severe discomfort."

cartilage and the cartilage could thus be less responsive to the effects of glucosamine. Additional studies are required to examine the effects of glucosamine treatment in patients with osteoarthritis of a longer duration.

Another reason for our negative results could be that 2 months of treatment was insufficient to effect clinical improvement in our patients. Other studies involving apparently healthier patients have found clinical improvement within 4-8 weeks of initiating treatment. The largest study of glucosamine identified significant benefit when it was compared with placebo at 4 weeks of treatment but not in the preceding weeks.[4] One trial found superior pain relief after 8 weeks of treatment with glucosamine when compared with ibuprofen.[2] The efficacy of glucosamine when given for longer than 8 weeks is uncertain.

Any trial that has a negative finding raises the prospect of a type II error. With 100 patients, we estimated that we would have an 80% chance of detecting a difference between the two groups of 1.1 points in scores on the visual analog scale. This would have represented a 31% reduction in pain scores at rest and a 21% reduction while walking when compared with placebo. It is difficult to assess what change in score is clinically significant when measuring the intensity of pain. One large study in which patients with knee osteoarthritis were treated with piroxicam used a 30% difference in scores as an indicator of efficacy[13]; piroxicam achieved this efficacy measure more often than placebo. Another large study using oxaprozin and nabumetone found a statistically significant 35% to 48% difference from baseline in scores on the visual analog scale.[14] We observed practically no difference between the groups when absolute visual analog scores were compared. There was a slight difference in favor of glucosamine when the change in score was compared with the score at rest, however, this did not approach statistical significance. We believe that a much larger cohort of patients would be necessary to achieve significance in a trial of this sort in a similar group of patients.

It is unclear whether the addition of chondroitin sulfate to glucosamine would have influenced the outcome of this study. This combination is available in health food stores and is advertised extensively. Chondroitin has been shown to stimulate the production of proteoglycans and hyaluronic acid and to inhibit the proteolytic enzymes which may damage cartilage.[15] Chondroitin has been shown to be more effective than placebo in reducing pain in patients with osteoarthritis of the knee.[16, 17] Only one controlled study has compared this combination with placebo in patients with osteoarthritis.[18] In this double-blind crossover study of 21 servicemen glucosamine with chondroitin was superior to placebo in reducing scores of pain intensity on the visual scale after 8 weeks of treatment. It is not clear if chondroitin contributed to the reduction in pain found in this study since other trials have suggested that 3-6 months of treatment are needed to derive any benefit from this compound. The National Institutes of Health are planning a study of 1000 patients that will compare the efficacy of glucosamine, glucosamine and chondroitin, and placebo in the treatment of osteoarthritis to clarify the role of combination treatment. In our patients with osteoarthritis of the knee glucosamine was no better than placebo in reducing the intensity of pain.

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COMMENTARY

Use of alternative products: where's the beef?

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The paper by Rindone et al raises interesting issues regarding the management of osteoarthritis (degenerative joint disease) using an alternative medicine. The authors do discuss some of the weaknesses of the study and point out that a larger controlled trial showed glucosamine to be superior to placebo. An additional drawback of the study is that over 50% of the patients were receiving other analgesics. Although there was no difference in analgesic use between the glucosamine and placebo group, it would be interesting to see if the patients that did not receive other analgesics might have had a better response to glucosamine. Despite the inherent weakness of the study, Rindone and colleagues should be credited with performing a "real world" clinical trial. I believe the results to be meaningful, and they should be used when counseling patients about the use of glucosamine.

Many clinicians are struggling to learn more about alternative practices and products, to understand better what patients are using and doing, and to provide rational advice and counseling about the use of alternative products. Eisenberg et al documented the rising use of alternative medicine in the 1990s, with over 12% of patients surveyed using at least one herbal product.[1] Less than half of patients are willing to disclose the use of these products to their physician. A more recent survey commissioned by the Kaiser Family Foundation showed that at least 50% of persons surveyed use a dietary supplement occasionally.[2]

Much speculation surrounds the reasons for the increasing use of alternative products. Although many clinicians likely prefer to ascribe this increased popularity to a populace being suckered by unscrupulous individuals, I believe the principal reason for patients seeking alternative therapy is their dissatisfaction with mainstream health care.

There is no question, however, that patients are being drawn to the use of alternative medicine because of the voluminous information made available about these products. Most of this information is, at best, unfiltered, a necdotal, and thinly disguised advertising. It is probably no coincidence that the development and popularity of the Internet has paralleled that of the alternative medicine movement. One need only research any alternative medicine product (glucosamine or any other) to be impressed with the sheer volume of information that is available to many of our patients. And it is clear that this industry is big business. Patients are spending over $40 billion per year on alternative products, some of whom cannot afford the added expense.

The passage of the 1994 Dietary Supplement Health and Education Act (DSHEA) has played a large role in the expanding use of alternative products. Under this statute, manufacturers of dietary supplements need not demonstrate the safety and efficacy of their products. The burden of proof to show a product is harmful was given to the Food and Drug Administration (FDA). Manufacturers of dietary supplements use thinly disguised indications to market their products (for example, "to promote liver health"). If one accepts that some of these products are pharmacologically active, it is not in the best interest of the public to have their safety so loosely regulated.

As with the study by Rindone et al, trials with popular alternative products are slowly being published in peer-reviewed journals, which is exactly what is needed. As we move toward a greater emphasis on evidence-based medicine, we must use these same principles in evaluating alternative products. Potential adulteration with toxic substances is an important consideration. One recent study showed a high frequency of adulteration with drugs or heavy metals in products imported from Asia.[3]

As with any drug, we cannot assume that any pharmacologically active substance is safe until evidence exists to that effect. Several published reviews identify alternative products known not to be safe.[4-7] What about interactions with conventional drugs? Other than a few known interactions (such as *Gingko biloba* and garlic increasing the risk of bleeding with warfarin), we know little about potential interactions. Suspected adverse reactions and drug interactions should be reported to the FDA MedWatch program.

How can the average clinician deal with these issues? We must realize that our patients are using alternative products and ask specifically about their use when obtaining a history. Clinicians need to be open-minded and understanding about patients' use of these products. One should review with the patient what evidence exists for a particular product. Ultimately, we will no longer be discussing alternative versus conventional treatment. We will discuss treatments that work and those that do not.[8] The "beef" is in the evidence.

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